and/or an increase in coadministered CBZ, could cause an imbalance in dopamine activity resulting in an NMS-like state in epileptic patients with organic brain comorbidity.

The patient was a 24-year-old man with severe mental retardation and symptomatic partial epilepsy. His electroencephalography showed a basic rhythm of high voltage 9–11 Hz predominantly in the occipital region, and occasional sharp waves in the right frontal, central, and parietal regions. Head computed tomography revealed no abnormality. Since his last secondarily generalized tonic–clonic seizure was observed at the age of 22, however, he has behaved violently toward his father. After that, he was referred to our psychiatric outpatient clinic. We determined that his violence could be associated with his epilepsy, and therefore gradually increased his ZNS dosage from 160 mg to 300 mg, resulting in a ZNS blood concentration of 35.6 ug/ml. This treatment resolved his complex partial seizure and initially decreased his violent impulses. However, his violent behavior returned, so we treated him with 3 mg/day of risperidon. This treatment had no effect and was quickly terminated. We then hypothesized that his violent outbursts could be a side effect of ZNS. Approximately two months after attempting risperidon, we stopped ZNS altogether and increased the CBZ dosage from 400 mg to 600 mg. He was also on a constant dosage of 1.6 mg clonazepam. On the fourth day of this new regimen, he became incontinent and drowsy and we advised him to begin taking ZNS again at a dosage of 300 mg/day. He gradually became agitated. After seven days, he was still agitated and suffered from sialorrhea, dysphagia, and choreiform movements such as retrocollis. His serum concentrations of ZNS and CBZ were 16.2 μg/ml and 8.7 μg/ml, respectively. On the 11th day he had a high fever (38.5°C), was perspiring heavily, and was excited. He was congenitally spastic, but we noted slightly increased muscle rigidity and the patient was no longer able to walk alone. He was immediately admitted to our psychiatric ward. We found no sign of infection or thyroid disease. Creatine phosphokinase (CK) was elevated to 1950 U/l (normal range: 62–287 U/l). His maximum CK level of 2826 U/l occurred the day after admission. Blood tests revealed that his white blood cell count (WBC) was 8200/mm^3 (his baseline WBC was approximately 4000/mm^3). C reactive protein was 0.04 mg/dl. Aspartate aminotransferase and alanine aminotransferase were 48 U/l (normal range: 10–33 U/l) and 27 U/l (normal range: 6–37 U/l), respectively. His blood pressure and heart rate were unstable, ranging from 130–170 to 65–100 mmHg and between 85 and 110/min, respectively. We diagnosed him with NMS-like state, and the medicines were all discontinued. Phenytoin (PHT) was administered intravenously. He was given 2000–3000 mL/day of fluids, but the high fever continued (38.5–39.2°C). On the day after admission, 40 mg/day of dantrolene was given intravenously. Subsequently the high fever gradually decreased. Within four days he was back at a normal body temperature, CK was 575 U/l, and all other laboratory tests were within normal limits. He became calm and his unstable blood pressure, heart rate, and diaphoresis all ceased. We concluded that he had recovered from his NMS-like state and dantrolene was discontinued.

DISCUSSION

In epileptic patients, ZNS exerts its anticonvulsant activities by blocking the spread or propagation of seizure discharges, just like PHT and CBZ (Leppik, 2004). Recently, a randomized controlled trial demonstrated that ZNS improves Parkinson's disease due to increased dopamine synthesis (Murata et al., 2007). ZNS could therefore cause an NMS-like state if the drug administration regimen leads to an imbalance in dopamine levels (Pope et al., 1986; Caroff and Mann, 1993).

In this patient, ZNS was abruptly discontinued while CBZ was simultaneously increased because we suspected that the violent behavior was probably caused by ZNS (Ettinger, 2006). We suspect that it was the sudden interruption of ZNS treatment that was mainly responsible for the initiation of the patient's NMS-like state. In addition, CBZ is a CYP3A4 inducer and accelerates the metabolism of ZNS, thereby promoting the development of the NMS-like state through a further decrease in ZNS blood concentration. In this case CBZ lowered the plasma level of ZNS nearly 50% in only three days, from 35.6 μg/ml to 16.2 μg/ml, despite the long half-life of ZNS (T1/2 = 63–69 h) (Leppik, 2004). The cerebral palsy may have also affected the developing NMS-like state, because organic brain disease and mental retardation are frequently seen in cases of NMS (Gurrera, 1999).

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REFERENCES

Caroff SN, Mann SC. (1993) Neuroleptic malignant syndrome. *Med Clin North Am* 77:185–202.

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Preferences of cancer patients regarding the disclosure of bad news

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Abstract

To understand patients' preferences regarding the disclosure of bad news is important in the clinical oncology setting. The aim of this study was to clarify descriptively the preferences of cancer patients. Five hundred and twenty-nine Japanese cancer outpatients were surveyed regarding their preferences regarding the disclosure of bad news, and several psychosocial and medical demographic variables were analyzed. In a descriptive analysis, more than 90% of the patients strongly preferred to discuss their current medical condition and treatment options with their physician and to have their physicians take the feelings of their family into consideration as well. While half of the patients preferred to receive information regarding their life expectancy, 30% preferred not to receive it. Multiple regression analyses indicated the preferences showing interindividual variations were associated with the level of education and the mental adjustment to cancer scores. A factor analysis revealed four preferences factors: method of disclosure of the bad news, provision of emotional support, provision of additional information, and setting. These four factors had good internal consistency reliability (Cronbach's alpha = 0.93–0.77). Providing emotional support, including the desire for the physician to show consideration for the patient's family, and understanding an individual's communication preferences may be useful for promoting patient–physician communication.

Keywords: patients' preference; bad news; communication; cancer; patient–physician relationship

Introduction

Bad news consists of any information likely to alter drastically a patient's view of his/her future [1] and includes information regarding diagnosis, recurrence, and treatment failure in clinical oncology settings. The communication skills of physicians delivering bad news about cancer can affect the degree of a patient's distress [2–4]. However, the majority of physicians do not have a standard strategy for delivering bad news to patients [5]. Furthermore, the majority of guidelines and interventions designed to enhance physicians' communication skills when delivering bad news, are based only on experts' opinions and do not have a strong theoretical basis [6,7], nor do they necessarily reflect the preferences of patients [8,9]. Consequently, enhanced communication skills do not always improve patients' experience [10]. Meanwhile, patients preferred communication features were linked with lower psychological distress and higher satisfaction levels [3]. Thus, future development of interventions in enhancing communication should include the patients' preferences and the theoretical framework of them [3,7]. However, information on the communication preferences of patients is insufficient, and present communication styles are restrictive and based on the opinions of experts.

Since the importance of providing individualized communication to patients has been recognized, medical and psychosocial predictive variables have been examined to determine their associations with patients' preferences [8,9,11]. In the US, [9] had surveyed cancer patients' preference when receiving their cancer diagnosis and suggested that patients'

preferences consisted of three factors, the content, support, and facilitation, which were associated with sex, age, and education. For physicians to tailor their communication style to individual patients, predictive variables for individual item of, rather than just factors of communication preferences, must be examined. Little attention, however, has been paid to this approach.

Cultural as well as social variables pertaining to both the patient and the physician determine the physicians' communication style. Many cultural aspects concerning the patient–physician relationship in oncology settings differ between Western and Asian countries [12,13]; for example, family-centered decision-making processes, the use of euphemisms, and physician paternalism are more common in Japan [14,15].

The accumulation of further study results on the cancer patients' preferences may help to refine current guidelines and establish patient-preference-based recommendations for dealing with this challenging task. Thus, the purpose of this study was to clarify patients' preferences regarding the disclosure of bad news concerning their cancer. To achieve this purpose, the present study assessed descriptive data, to explore the components of patients' preferences, and to identify the variables associated with communication style preferences. A self-reported questionnaire was utilized to identify patients' desires regarding their physicians' communication style when delivering bad news; this questionnaire was based on previously conducted in-depth interviews with patients and their physicians [15].

Materials and methods

Patients

All the subjects were cancer outpatients who were attending follow-up medical appointments at the National Cancer Center (NCC) Hospital East in Japan, which treat mainly breast, digestive, head and neck, and lung cancer. The eligibility criteria were: patients who were deemed by their physician and their medical chart to have received bad news regarding cancer three or more months earlier, including news of diagnosis, recurrence, disease progression, or the absence of an active anticancer treatment; patients who were 20 years old or older; patients who were judged by their physician to be capable of completing the survey; and patients who were capable of understanding spoken and written Japanese.

Procedure

The Institutional Review Board and the Ethics Committee of the NCC, Japan approved this study, and each patient provided an informed written consent.

All eligible outpatients were consecutively invited to participate in the study after their follow-up medical visit. The patients completed a series of questionnaires, and mailed them back. If the questionnaires contained any blanks, a single attempt was made to obtain the missing information by telephone or post.

Measurements

Patients' preferences regarding the communication style of physicians delivering bad news about cancer. The preference questionnaire consisted of 70 communication styles of physicians disclosing bad news about cancer. The survey items were generated on the basis of previously conducted in-depth interviews with patients and their physicians [15], a systematic literature review, and discussions among authors, and included a broad range of communication styles. The instrument was piloted among 12 cancer patients. These patients responded to each item and provided feedback on the content, clarification, and format of the items. Minor revisions were made in response to their feedback.

The participants were asked to choose the responses that best reflected how they would like to be told if they were to receive bad news, such as the diagnosis of cancer, recurrence, or progression of cancer (scored on a five-point Likert scale; 1: strongly do not prefer–5: strongly prefer).

Demographic and medical characteristics. The questionnaire included demographic data, including age, sex, employment status, education, marital status, and social support. Medical data, such as the type of cancer, recurrence or metastasis, current anticancer treatment, received bad news, and the period after the latest bad news, were obtained from the patients' medical records.

Mental Adjustment to Cancer (MAC) scale [16]. The Japanese version of the MAC scale [17] is a standardized instrument for evaluating the adjustment of patients to their cancer. The MAC scale consists of 40 items in 5 subscales: fighting-spirit (16 items), anxious-preoccupation (nine items), helplessness-hopelessness (six items), fatalism (eight items), and avoidance (one item). Each item is rated on a 4-point Likert scale (1–4).

Hospital Anxiety and Depression Scale (HADS) [18]. The Japanese version of the HADS [19] is a standardized instrument for evaluating anxiety and depression. The HADS consists of 14 items in 2 subscales: anxiety and depression. Each item is rated on a 4-point Likert scale (0–3).

Data analysis

First, we assessed the distribution of the patients' responses for all the 70 items in the questionnaire. Second, we grouped the five response categories into three categories: 'prefer', 'do not prefer', and 'no preference either way'. The items for which more than 20% of the respondents chose both 'prefer' and 'do not prefer' were arbitrarily defined as communication style preferences with high interindividual variations. We performed multiple regression analyses configured using the stepwise method to investigate associations with demographic characteristics, medical characteristics, and psychological status as independent variables, and communication styles with interindividual variations as dependent variables. Third, we performed an explanatory factor analysis using the maximum-likelihood method with promax rotation to identify potential components of the patients' preferences, because we did not have any hypothesis. Four factors were adopted on the basis of a screeplot (the eigenvalues of 3-, 4-, 5-, 6-and 7-factor were 4.68, 2.67, 1.98, 1.70, and 1.45, respectively) and interpretable, and the Cronbach's alpha value was calculated to evaluate the internal consistent reliability of each factor. Significance was defined as $p < 0.05$. SPSS software, version 12.0, was used to perform the statistical analysis.

Results

Patients

One thousand and fifty-six consecutive outpatients were screened for inclusion. Of the 656 patients who were eligible, 34 refused the approach, 15 could not be contacted, and 32 were lost to contact. Of the remaining 575 patients who were approached, 9 refused to participate and 529 (93.5%) returned the questionnaire. Overall, 80.6% (529/656) of the eligible patients participated in the present study. The demographic characteristics of the participants are listed in Table 1.

Table 1. Demographic characteristics of the subjects ($N = 529$)

		N	%
Age (years; mean, S.D. range)	62, 11, 26–97		
Sex	Male	274	51.8
	Female	255	48.2
Employmental status	Employed	190	35.9
	Unemployed	339	64.1
Marital status	Married	452	85.4
	Unmarried	77	14.6
Household size	Living alone	19	3.6
	2 or more	510	96.4
Education	9 or less years	98	18.6
	10 or more years	430	81.4
Cancer site	Digestive	185	34.7
	Breast	125	23.5
	Head and neck	112	21.2
	Lung	107	20.2
Recurrence or metastasis	Presence	299	56.6
	Absence	229	43.4
Treatment received	Surgery	426	80.5
	Chemotherapy	221	41.8
	Radiation therapy	153	28.9
	Hormone therapy	45	8.5
	Other	16	3.0
Current anticancer treatment	Presence	134	25.5
	Absence	395	74.5
Bad news received regarding			
Diagnosis	Yes	529	100
	No	0	0
Recurrence	Yes	164	31.0
	No	365	69.0
Disease progression	Yes	38	7.0
	No	491	93.0
Absence of active anticancer treatment	Yes	1	0.2
	No	528	99.8

Table 2. Descriptive data on patinets' preferences for communication when receiving bad news ($N = 529$)

Item	Mean	SD	Strongly prefer %	Prefer %	No preference either way %	Do not prefer %	Strongly do not prefer %
Telling the treatment plan	4.53	0.58	56.5	40.8	2.1	0.4	0.2
Assuming responsibility for your care until the end	4.51	0.59	55.6	41.0	2.6	0.8	0.0
Answering your questions	4.49	0.52	49.5	49.7	0.8	0.0	0.0
Telling about the latest treatment	4.49	0.63	54.4	41.4	3.0	0.8	0.4
Breaking bad news in a way that is easy to understand	4.43	0.54	45.6	52.4	2.1	0.0	0.0
Telling about all treatment options available to you	4.42	0.69	51.0	42.2	4.7	1.9	0.2
Explaining the status of your illness	4.40	0.56	42.9	54.4	2.1	0.6	0.0
Breaking bad news honestly	4.35	0.58	38.9	57.7	2.6	0.6	0.2
Telling what you can hope for	4.35	0.64	43.3	49.1	7.0	0.4	0.2
Explaining until you are satisfied	4.34	0.63	41.4	52.2	5.3	1.1	0.0
Telling the recommended treatment	4.33	0.61	39.1	56.0	3.8	1.1	0.0
Explaining the risks and side effects of treatment	4.33	0.75	44.8	48.4	2.5	4.0	0.4
Explaining the progression of disease	4.31	0.61	37.4	58.0	2.8	1.7	0.0
Using actual images and test data	4.30	0.70	41.0	51.0	5.1	2.6	0.2
Communicating clearly the main points of bad news	4.28	0.62	34.8	60.9	2.5	1.5	0.4
Telling the prospects of cancer cure	4.28	0.65	37.1	55.0	6.8	0.9	0.2
Explaining the symptoms	4.27	0.59	32.7	62.8	3.2	1.1	0.2
Checking to see that you understand	4.24	0.74	36.3	55.6	4.9	1.9	1.3
Taking sufficient time	4.23	0.74	38.4	48.6	10.8	2.1	0.2
Breaking bad news in detail	4.22	0.79	39.1	49.0	7.0	4.5	0.4
Breaking bad news in precise terms	4.17	0.72	30.2	60.9	7	4.5	0.4
Telling in a way with hope	4.17	0.74	33.1	54.4	10.2	1.3	0.9
Talking gently.	4.16	0.76	33.8	52.0	11.3	2.1	0.8
Being a trusting physician	4.14	0.77	33.3	50.7	13.2	2.3	0.6
Breaking bad news in a sympathetic manner	4.11	0.76	31.2	52.7	12.7	3.0	0.4
Discussing your everyday life and work in the future	4.11	0.71	28.2	56.7	12.7	2.5	0.0
Giving papers that physician referred to	4.10	0.79	30.6	54.1	10.6	4.0	0.8
Showing the same concern for your family as for you	4.10	0.73	29.1	55.0	13.2	2.3	0.4
Breaking bad news in a courteous manner	4.09	0.75	29.3	53.7	13.6	3.4	0.0
Breaking bad news in a private setting	4.09	0.78	31.0	50.1	16.4	1.5	0.9
Telling with concern for your feelings	4.04	0.89	31.0	50.9	11.2	5.1	1.9
Breaking bad news in a setting with family	4.02	0.82	28.9	49.1	17.4	4.0	0.6
Telling all the bad news	3.99	0.85	27.4	51.8	13.6	6.6	0.6
Writing on paper to explain	3.98	0.88	27.6	51.8	13.4	5.7	1.5
Saying, 'Let's fight this together'	3.96	0.78	24.2	51.2	21.6	2.5	0.6
Speaking words of encouragement	3.96	0.82	25.3	50.7	19.5	3.6	0.9
Providing information on services and support	3.96	0.73	21.4	56.9	19.1	2.1	0.6
Looking at your eyes and face	3.94	0.84	23.0	55.4	15.7	4.1	1.7
Explaining a second opinion	3.93	0.85	26.5	45.7	23.3	3.8	0.8
Checking questions	3.91	0.83	22.1	54.3	17.4	5.3	0.9
Accepting your expressing emotions	3.89	0.77	20.2	53.1	21.9	4.7	0.0
Saying, 'You're OK'	3.86	0.86	22.7	47.3	23.8	5.5	0.8
Saying words that soothe your feelings	3.79	0.80	16.3	53.1	25.5	4.0	1.1
Saying words to prepare mentally	3.78	0.79	15.5	53.5	25.5	4.7	0.8
Giving specialized medical information	3.74	0.85	16.1	50.1	27.2	4.9	1.7
Physician deciding on the method of treatment	3.68	0.97	16.8	52.4	13.6	16.3	0.9
Answering your questions about alternative medicine	3.66	0.94	15.7	49.0	24.4	7.9	3.0
Ensuring that the telephone does not ring	3.62	0.92	16.8	39.5	35.5	5.5	2.6
Telling frequent questions	3.44	0.92	10.6	39.5	35.7	11.7	2.5
Asking how much you know about your illness before breaking bad news	3.44	0.84	7.4	43.5	36.3	11.3	1.5
Breaking bad news using euphemisms	3.42	0.98	11.3	39.5	32.3	13.0	3.8
Telling about your life expectancy	**3.28**	**1.18**	**14.7**	**35.7**	**19.7**	**22.7**	**7.2**
Not using the word 'cancer' repeatedly	3.23	0.86	7.4	26.1	51.6	12.1	2.8
Telling how to obtain information (e.g. books or the Internet)	3.22	0.94	8.1	28.9	44.0	14.6	4.3
Breaking bad news in a matter-of-fact manner	**2.90**	**1.09**	**5.3**	**29.7**	**23.3**	**33.1**	**8.7**
Breaking bad news step-by-step	**2.84**	**1.12**	**7.2**	**24.6**	**21.9**	**37.2**	**9.1**
Other caregivers attending (e.g. other physicians, or nurses)	2.79	0.90	2.8	14.7	50.1	23.6	8.7
Talking in a decisive tone of voice	**2.65**	**0.97**	**3.2**	**17.4**	**28.9**	**42.0**	**8.5**
Breaking bad news before it is definite	**2.60**	**1.06**	**2.8**	**24.0**	**14.7**	**46.9**	**11.5**
Breaking bad news only to you	2.33	0.97	2.3	10.8	23.4	45.2	18.3

Table 2. (*continued*)

Item	Mean	SD	Strongly prefer %	Prefer %	No preference either way %	Do not prefer %	Strongly do not prefer %
Touching your hand or shoulder	2.31	0.85	0.8	5.9	34.6	41.2	17.6
Talking at physician's pace	2.20	1.02	1.1	13.2	17.2	41.8	26.6
A physician at the first meeting breaking bad news	2.18	0.97	1.3	8.5	24.0	39.5	26.7
Breaking bad news to your family first	2.15	0.91	1.5	6.0	22.7	45.7	24.0
Using technical words	2.13	0.81	1.7	9.8	15.4	45.4	27.5
Telling only bad news	2.01	0.91	0.8	8.3	12.5	48.2	30.1
Talking in a business-like manner	1.99	0.80	0.2	5.3	14.4	53.3	26.8
Breaking bad news by telephone	1.68	0.73	0.4	2.3	6.6	46.3	44.4
Dealing with your questions in an irritated manner	1.43	0.55	0.0	0.2	2.1	38.0	59.7
Breaking bad news in a vague manner	1.37	0.59	0.4	0.8	0.9	31.8	66.2

Bold: The items for which more than 20% of respondents chose both prefer or strongly prefer and do not prefer or do not.

Table 3. Variables associated with communication styles with interindividual variations ($N = 526$)

Independent variables	Beta	*P*	*R*	R^2	Adjusted R^2
Telling about your life expectancy.				0.034	0.028
Marital status (No/yes)[a]	0.132	0.003	0.131		
Helplessness/hopelessness	−0.097	0.027	−0.096		
Education (Year)	0.089	0.047	0.087		
Breaking bad news in a matter-of-fact manner				0.112	0.104
Age (Year)	0.163	<0.001	0.153		
Education (Year)	0.161	<0.001	0.158		
Fatalism	0.144	0.003	0.129		
Anxious preoccupation	−0.130	0.004	−0.125		
Recurrence or metastasis (No/yes)[a]	0.086	0.048	0.087		
Breaking bad news step-by-step				0.112	0.103
Fighting spirit	0.153	<0.001	0.153		
Education (Year)	−0.150	<0.001	−0.153		
Employment status (No/yes)[a]	−0.122	<0.001	−0.125		
Avoidance	0.121	0.006	0.121		
The number of received bad news (0–4)	0.097	0.020	0.102		
Breaking bad news before it is definite				0.030	0.024
Avoidance	0.119	0.007	0.118		
Education (Year)	0.098	0.026	0.097		
Breast cancer (No/yes)[a]	−0.086	0.048	−0.086		
Talking in a decisive tone of voice				0.050	0.044
Sex[b]	−0.169	<0.001	−0.168		
Fatalism	0.099	0.027	0.097		
Education (Year)	−0.091	0.042	−0.089		

[a] Coded as 0 = no, 1 = yes.
[b] Coded as 0 = male, 1 = female.

Communication styles preferred by most patients and communication style preferences with interindividual variations

Descriptive data of each item are shown in Table 2. The communication styles preferred by most patients were as follows: physicians should discuss their treatment with them and establish a rapport with them. On the other hand, some communication styles were not preferred by most patients. For example, physicians deal with patients' questions in an irritated manner and break bad news in a vague manner. Furthermore, the communication style preferences with interindividual variations were as follows: the desire for information regarding the patient's life expectancy, the desire to receive bad news in a matter-of-fact manner, the desire to receive bad news gradually, the desire to receive bad news in a decisive tone of voice, and the desire to receive bad news even before diagnosis is definite.

Variables associated with communication style preferences with interindividual variations

Table 3 lists the multiple regression models for each item which exhibited high interindividual variations (indicated in bold in Table 2). Three participants were excluded from this statistical analysis because of missing data. Married patients,

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patients with less helplessness/hopelessness, and patients with more formal education preferred to talk about their life expectancy with their physicians. Older patients, patients with more formal education, patients with more fatalism and less anxious preoccupation, and patients with recurrence or metastasis preferred that their physicians break the bad news in a matter-of-fact manner. Patients with more fighting spirit, less formal education, employed patients, patients with more avoidance, and patients who received a more large number of bad news preferred that their physicians break the bad news in a step-by-step manner. Patients with more avoidance, patients with more formal education, and patients with breast cancer preferred that their physicians break the bad news before a definite diagnosis had been made. Female patients, patients with more fatalism, and patients with less formal education preferred that their physicians talk in a decisive tone of voice.

Components of the patients' preferences regarding the communication style of the physicians disclosing bad news about cancer

The results of the exploratory factor analysis yielded four components (Table 4). The correlation coefficients between each factor were weak to moderate ($r = -0.20-0.50$). Factor 1: Method of disclosure of bad news (21 items, variance explained = 9.81, alpha coefficient = 0.93). This factor pertained to how physicians delivered bad news to patients during consultations. Factor 2: Provision of emotional support (17 items, variance explained = 7.77, alpha coefficient = 0.88). This factor covered the supportive aspects of the communication and included offering comfort and support to the patient. Factor 3: Provision of additional information (15 items, variance explained = 5.17, alpha coefficient = 0.82). This factor dealt with the additional information delivered by physicians during consultations while breaking bad news. Factor 4: Setting (17 items, variance explained = 10.23, alpha coefficient = 0.77). This factor focused on the fundamental communication skills of the physicians while delivering bad news.

Discussion

The communication styles preferred by the majority of the patients might be recommended to physicians delivering bad news to patients; physicians should deliver both positive (e.g. treatment plan and what patient can hope for) and negative (e.g. risk and side effect of treatment) information pertaining to the disease and its treatment and should also adopt a supportive attitude. Continuing physician responsibility for patient care and future treatment plans were the most preferred attitudes and vagueness was the least preferred attitudes from the patients' perspectives. These findings suggest that engagement between the patients and their physicians is important when bad news is being broken.

Not all but many of the items pertaining to the communication styles preferred by most patients were consistent with those published in previous general guidelines and recommendations, for example, discussion of the possible treatment options with the patient, provision of warning signals, and delivery of the diagnosis to the patient honestly and in simple language, but not bluntly [20,7]. However, some of the items preferred by most patients or with high interindividual variations were not consistent with previously published guidelines and recommendations. For example, only 6.7% of patients wanted their physician to touch their hands or shoulders when delivering bad news, although Ptacek and Eberhardt [20] reported the benefit of touch.

Consistent with the findings in the previous report [21], patients responded with a high interindividual variation in preferences for discussing life expectancy. Furthermore, about half of the patients in the present study did not want physicians to deliver bad news step-by-step, a recommended communication style [5]. About one quarter of the patients in the present study preferred communication styles in which physicians delivered the bad news even before the content of the news was definite, a communication style that was not recommended in the previous report [6]. These results suggest the importance of communicating with patients on an individual basis.

Furthermore, while patients preferred to be clearly told of their diagnosis, half of them preferred that physicians use euphemisms and 33.5% of them preferred that physicians do not repeatedly use the word 'cancer'. As we checked on the accuracy of patients' understanding of each item in the pilot survey, we think there is little possibility of misunderstanding the item's meaning. These results do not support the guidelines recommended for using the word 'cancer' and avoiding euphemisms in order not to cause a misunderstanding [7,20]. Japanese physicians use more euphemisms when delivering bad news to patients than Western physicians [13,22], and the word, 'cancer' might have a psychologically invasive impact on patients with cancer in Japan. Therefore, the use of euphemisms may give patients the impression that their physician is supporting them emotionally; these items were included in the emotional support factor.

Interestingly, 84% of the patients preferred to have their physicians show the same concern for the feelings of their family as for themselves. This

Table 4. Components of the patients' preferences for communication when receiving bad news: a factor analysis ($N = 529$)

Factor 1: Method of disclosure of bad news	*Factor loading*
Breaking bad news honestly	0.757
Breaking bad news in a way that is easy to understand	0.719
Explaining the progression of disease	0.704
Explaining the status of your illness	0.670
Telling all the bad news	0.666
Breaking bad news in precise terms	0.660
Explaining the symptoms	0.644
Communicating clearly the main points of bad news	0.612
Using actual images and test data	0.593
Telling the recommended treatment	0.584
Explaining until you are satisfied	0.563
Breaking bad news in detail	0.556
Answering your questions	0.547
Breaking bad news in a courteous manner	0.542
Giving papers that physician referred to	0.524
Being a trusting physician	0.454
Assuming responsibility for your care until the end	0.422
Writing on paper to explain	0.405
Telling the prospects of cancer cure	0.404
Looking at your eyes and face	0.380
Telling about your life expectancy	0.363
Factor 2: Provision of emotional support	
Saying words that soothe your feelings	0.675
Saying, 'You're OK'	0.673
Saying, 'Let's fight this together'	0.667
Telling in a way with hope	0.662
Talking gently	0.609
Speaking words of encouragement	0.599
Telling what you can hope for	0.560
Saying words to prepare mentally	0.542
Breaking bad news in using euphemisms	0.525
Breaking bad news in a sympathetic manner	0.473
Showing the same concern for your family as for you	0.455
Breaking bad news step-by-step	0.421
Telling with concern for your feelings	0.394
Accepting your expressing emotions	0.380
Checking questions	0.309
Breaking bad news in a setting with family	0.294
Not using the word 'cancer' repeatedly	0.263
Factor 3: Provision of additional information	
Telling the treatment plan	0.543
Telling about all treatment options available to you	0.532
Telling about the latest treatment	0.513
Explaining the risks and side effects of treatment	0.490
Explaining a second opinion	0.481
Giving specialized medical information	0.478
Taking sufficient time	0.472
Telling frequent questions	0.447
Telling how to obtain information (e.g., books or the Internet)	0.434
Checking to see that you understand	0.434
Talking about alternative medicine	0.431
Providing information on services and support	0.386
Breaking bad news in a private setting	0.385
Discussing your everyday life and work in the future	0.349
Asking how much you know about your illness before breaking bad news	0.297
Factor 4: Setting	
Breaking bad news by telephone.	0.639
Telling only bad news	0.573
Talking at physician's pace	0.549
Dealing with your questions in an irritated manner	0.545
Breaking bad news in a vague manner	0.524
A physician at the first meeting breaking bad news	0.488
Talking in a business-like manner	0.475
Using technical words	0.447
Breaking bad news in a matter-of-fact manner	0.420
Talking in a decisive tone of voice	0.416
Touching your hand or shoulder	0.391
Breaking bad news only to you	0.388
Breaking bad news your family first	0.361
Physician deciding on the method of treatment	0.322
Breaking bad news before it is definite	0.320
Providing information on services and support	0.301
Ensuring that the telephone does not ring	−0.232

finding might be related to the distress experienced by the families of cancer patients after diagnosis, treatment, or the appearance of adverse effects [23]. Another explanation for this finding might be related to Asian culture. In Japan, families and physicians have been accorded a larger role in clinical decision making, and a patient's family is usually informed of an incurable cancer diagnosis before the patients has been notified [12]. That is to say, the family might experience distress before the patient does. Therefore, patients might desire for their physicians to show concern for the feelings of their family.

In the present study, 78% of the patients preferred to be with their family when the bad news was being broken and 14% of the patients preferred to receive bad news at their physicians' pace. Although some previous studies in Western countries have recommended that bad news should be delivered at the patients' pace to increase the patients' sense of control, physicians should recognize that many Japanese cancer patients prefer to play a collaborative role in the decision making process, rather than assuming active and passive roles, and will respect the physician's opinion even if the physician's recommendation conflicts with their own wishes [14].

This study also showed that 85% of patients preferred not only to discuss the bad news but also to talk about the impact of their disease on their daily activities, the information of a second opinion (72.2%), and complementary and alternative medicine (64.7%), although previous studies have not adequately addressed whether other information should be given by physicians to patients during the consultation. Physicians might be encouraged to discuss such matters with their patients.

Previous studies [8,9,11] reported that age, sex, level of education, and medical condition are significantly associated with preferred communication styles. In the present study, marital status, employment status, psychological adjustment,

the number of bad news, and medical status were also associated with patients' preferences, while psychological distress and social support were not associated with them. However, all the independent variables in this study had small standardized partial regression coefficients in each regression model, and all the multiple regression models showed a low proportion of variance. Thus, communication preferences with interindividual variations are difficult to identify on the basis of the patients' medical and psychosocial data alone, so physicians should try to understand each patient's preferences and tailor their communication style to meet the needs of individual patients.

The exploratory factor analysis in the present study identified four separate, internally reliable factors related to the communication style of physicians disclosing bad news. These factors were fundamentally based on the results of our previous qualitative study [15]. Parker *et al.* [9] reported a 3-factor structure; what and how much information, emotional support, and setting. Our present study supported the report by Parker *et al.* Furthermore, the factor structure of the present study also independently identified the provision of additional information factor, and this factor was not identified in the report by Parker *et al.* This difference can probably be attributed to the fact that the design of the two studies differed; we collected the survey items in the present study based on a previous analysis of several interviews [15], while Parker *et al.* [9] collected their survey items based on the opinions of experts, including oncologists and psychooncologists, and a literature review.

The result of the factor analysis provide a framework for devising interventions to enhance physicians' communication skills, that is, physicians may be taught how to disclose bad news in a manner that corresponds to an individual patient's preferences. As far as we know, no communication skills training programs based on patients' preferences have been reported. In the future, it would be desirable to design intervention programs based on the frameworks thus identified. Furthermore, future study to model the relationship between each factor of the patients' preferences and psychosocial and medical characteristics, based on the results of this exploratory factor analysis, is needed.

Two limitations of the present study should be noted. First, we conducted the study at a single teaching cancer center. Thus, the results of this study might not be representative of other cancer centers. Nonetheless, because the consecutive sample included patients with a variety of cancers, stages of disease, and from several age groups, of both genders, with several different psychosocial characteristics, we believe that our results reflect the preferences of a broad range of patients. The second limitation is that our study examined the preferences of patients at only one point in time, and not over time. Thus, we cannot speculate on the stability of the measurements used in this study. The informational needs of patients have been reported to change over the course of their treatment. [11] Because of the cross-sectional nature of this study, we did not attempt to formally address this question. However, significant differences were partially found between patients without and those with tumor recurrence or metastasis.

In conclusion, while the preferences of patients in Japan are mostly similar to those of patients in Western countries, some communication, for example, the desire for the physician to show consideration for the patient's family, seems to be particularly important to patients in Japan. Although communication style preferences with interindividual variations are difficult to identify based on medical and psychosocial data alone, understanding an individual's communication preferences may be useful for promoting patient–physician communication.

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References

1. Buckman R. Breaking bad news: why is it still so difficult? *Br Med J* 1984;**288**:1597–1599.
2. Takayama T, Yamazaki Y, Katsumata N. Relationship between outpatients' perceptions of physicians' communication styles and patients' anxiety levels in a Japanese oncology setting. *Soc Sci Med* 2001;**53**:1335–1350.
3. Schofield PE, Butow PN, Thompson JF *et al.* Psychological responses of patients receiving a diagnosis of cancer. *Ann Oncol* 2003;**14**:48–56.
4. Morita T, Akechi T, Ikenaga Y *et al.* Communication about the ending of anticancer treatment and transition to palliative care. *Ann Oncol* 2004;**15**:1551–1557.
5. Baile WF, Buckman R, Lenzi R, Glober G, Beale EA, Kudelka AP. SPIKES-A six-step protocol for delivering bad news: application to the patient with cancer. *Oncologist* 2000;**5**:302–311.
6. Girgis A, Sanson-Fisher RW, Schofield MJ. Is there consensus between breast cancer patients and providers on guidelines for breaking bad news? *Behav Med* 1999;**25**:69–77.
7. Cegala DJ, Lenzmeier Broz S. Physician communication skills training: a review of theoretical backgrounds, objectives and skills. *Med Educ* 2002;**36**:1004–1016.
8. Butow PN, Kazemi JN, Beeney LJ, Griffin AM, Dunn SM, Tattersall MH. When the diagnosis is cancer: patient communication experiences and preferences. *Cancer* 1996;**77**:2630–2637.
9. Parker PA, Baile WF, de Moor C, Lenzi R, Kudelka AP, Cohen L. Breaking bad news about cancer: patients' preferences for communication. *J Clin Oncol* 2001;**19**: 2049–2056.

10. Shilling V, Jenkins V, Fallowfield L. Factors affecting patient and clinician satisfaction with the clinical consultation: can communication skills training for clinicians improve satisfaction? *Psycho-Oncology* 2003; **12**:599–611.
11. Butow PN, Maclean M, Dunn SM, Tattersall MH, Boyer MJ. The dynamics of change: cancer patients' preferences for information, involvement and support. *Ann Oncol* 1997;**8**:857–863.
12. Ruhnke GW, Wilson SR, Akamatsu T *et al.* Ethical decision making and patient autonomy: a comparison of physicians and patients in Japan and the United States. *Chest* 2000;**118**:1172–1182.
13. Baile WF, Lenzi R, Parker PA, Buckman R, Cohen L. Oncologists' attitudes toward and practices in giving bad news: an exploratory study. *J Clin Oncol* 2002;**20**: 2189–2196.
14. Sekimoto M, Asai A, Ohnishi M *et al.* Patients' preferences for involvement in treatment decision making in Japan. *BMC Fam Pract* 2004;**5**:1.
15. Fujimori M, Akechi T, Akizuki N *et al.* Good communication when receiving bad news about Cancer in Japan. *Psycho-Oncology* 2005;**14**:1043–1051.
16. Watson M, Greer S, Young J, Inayat Q, Burgess C, Robertson B. Development of a questionnaire measure of adjustment to cancer: the MAC scale. *Psychol Med* 1988;**18**:203–209.
17. Akechi T, Fukue-Saeki M, Kugaya A *et al.* Psychometric properties of the Japanese version of the Mental Adjustment to Cancer (MAC) scale. *Psycho-Oncology* 2000;**9**:395–401.
18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**: 361–370.
19. Kugaya A, Akechi T, Okuyama T, Okamura H, Uchitomi Y. Screening for psychological distress in Japanese cancer patients. *Jpn J Clin Oncol* 1998;**28**: 333–338.
20. Ptacek JT, Eberhardt TL. Breaking bad news. A review of the literature. *JAMA* 1996;**276**:496–502.
21. Hagerty RG, Butow PN, Ellis PA *et al.* Cancer patient preferences for communication of prognosis in the metastatic setting. *J Clin Oncol* 2004;**22**:1721–1730.
22. Holland JC, Geary N, Marchini A, Tross S. An international survey of physician attitudes and practice in regard to revealing the diagnosis of cancer. *Cancer Invest* 1987;**5**:151–154.
23. Resendes LA, McCorkle R. Spousal responses to prostate cancer: an integrative review. *Cancer Investigation* 2006;**24**:192–198.

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fluid intake and in patients with excessive somnolence. Hyperammonemic encephalopathy should be suspected, and ammonia levels should be measured if unexplained lethargy and/or vomiting develop. Patients also need to be monitored for dizziness and falls. Controlled clinical trials are needed to assess the safety and efficacy of intravenous valproate in the treatment of uncontrollable aggression.

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REFERENCES

1. Jacupcak M, Tull MT. Effects of trauma exposure on anger, aggression, and violence in a nonclinical sample. *Violence Vict.* 2005; 20:589–598.
2. Miller MM, McEwen BS. Establishing an agenda for translational research in PTSD. *Ann N Y Acad Sci.* 2006;1071:294–312.
3. Del Bello MP, Caleb A, Strakowski M. Divalproex for the treatment of aggression associated with adolescent mania. *J Child Adolesc Psychopharmacol.* 2004;14:325–328.
4. Barzman DH, McConville BJ, Masterson B, et al. Impulsive aggression with irritability and responsive to divalproex: a pediatric bipolar spectrum disorder phenotype? *J Affect Disord.* 2005;88:279–285.
5. Hilty DM, Rodriguez GD, Hales RE. Intravenous valproate for rapid stabilization of agitation in neuropsychiatric disorders. *J Neuropsychiatry Clin Neurosci.* 1998;10:365–366.
6. Kaltsounis J, De León OA. Intravenous valproate treatment of severe manic symptoms after gastric bypass surgery. A case report. *Psychosomatics.* 2000;41:454–456.
7. Hellings JA, Weckbaugh M, Nickel EJ, et al. A double-blind, placebo-controlled study of valproate for aggression in youth with pervasive developmental disorders. *J Child Adolesc Psychopharmacol.* 2005;15:682–692.
8. Citrome L, Casey DE, Daniel DG, et al. Adjunctive divalproex and hostility among patients with schizophrenia receiving olanzapine or risperidone. *Psychiatr Serv.* 2004;55: 290–294.
9. Lott AD, McElroy SL, Keys MA. Valproate in the treatment of Behavioral agitation in elderly patients with dementia. *J Neuropsychiatry Clin Neurosci.* 1995;7:314–319.
10. Puglisi-Allegra S, Simler S, Kempf E, et al. Involvement of the GABA-ergic system on shock-induced aggressive behavior in two strains of mice. *Pharmacol Biochem Behav.* 1981;14: 13–18.
11. Maes M, Calabrese J, Jayathilake K, et al. Effects of subchronic treatment with valproate on l-5-HTP-induced cortisol responses in mania: evidence for increased central serotonergic neurotransmission. *Psychiatry Res.* 1997; 71:67–76.

Evidence-Based Guidelines for Interpretation of the Hamilton Rating Scale for Depression

To the Editors:

Interpretation of a psychiatric rating scale is often not self-evident. Most of the rating scales serve 2 purposes, namely to measure disease severity and to measure change in severity.[1] Correspondingly, clinicians need guidelines to help interpret the scores of a rating scale; to know how severe a patient is when the score is, say, 20; and also to know how much better a patient has become when the score has decreased, say, from 20 to 15.

When a new rating scale is developed and introduced, however, the first set of publications give details on their reliability and validity but usually fail to provide guidelines on how to interpret the scores. The situation is unfortunately more or less the same with the more classic and widely used rating scales such as the Hamilton Rating Scale for Depression (HAM-D) or the Brief Psychiatric Rating Scale (BPRS). Thus, until very recently, it had never been analyzed how ill a patient with a BPRS total score of 30, 50, or 90 actually is from a clinical point of view, nor had the definition of "response" ever been any better than arbitrary as various studies defined response as a reduction of 20%, 30%, 40%, or 50%.[2]

One solution to increase interpretability of a psychiatric rating scale is the so-called anchor-based approach,[1] by which a new instrument is compared with an independent standard or anchor that is itself interpretable and at least moderately correlated with the instrument being explored. Leucht et al[2] adopted this approach for the BPRS by comparing it with the Clinical Global Impression (CGI) scales[3] that are by themselves informative and interpretable as they describe a patient's overall clinical state as a "global impression" by the rater. They thus established that a BPRS total score of 31, 41, and 53 approximately signified "mildly, moderately, and markedly ill," respectively. To be judged "much improved," the BPRS had to be reduced by around 50%.[2]

For the HAM-D, the literature has been a little bit more informative, and we have the overall consensus that a score of 7 or 8 is the cutoff between asymptomatic and symptomatic statuses[4] and that a response is most often defined as 50% or greater reduction in the total score.[5] However, to date, little empirical research has been conducted on these expert opinion–based definitions.[6] The present paper aims to apply the anchor-based approach to the HAM-D to provide an evidence-based guideline for interpretation of this de facto international gold standard for assessing severity and change in severity of depression.[7]

We pooled original patient data from 7 clinical trials of acute phase treatment of major depression (baseline n = 1927; 59.0% women; average age, 41.8 years; SD, 12.6) with imipramine, amitriptyline, trazodone, fluoxetine, paroxetine, fluvoxamine, or placebo that used the 17-item HAM-D[8] and the CGI scales[3] (Table 1). Five of them were conducted in Japan and 2 in the United States, but there were no substantive or meaningful differences in the demographic or clinical characteristics of the participating patients between the 2 countries, and the data were combined in the following analyses. All the trials lasted between 6 and 13 weeks. All trials required minimum scores as eligibility criterion to assure that the patients were symptomatic at treatment commencement. The mean HAM-D score in all studies combined was 22.8 (SD, 4.4) at baseline and 10.2 (SD, 8.7) at end point.

Five trials administered the CGI-S (n = 1561), and 5 trials administered the CGI-C scales (n = 1212). The CGI-S assesses the clinician's impression of the patient's current illness state, and the following scores can be given: 1 = normal/not at all ill, 2 = borderline/mentally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 =

TABLE 1. Demographic and Clinical Characteristics of the 7 Included Trials

Trial	Country	n	Age	Sex (Female, %)	Baseline HAM-D	Baseline CGI-S	CGI-C	Comparator
1	Japan	216	46.5 (13.8)	53.7	23.9 (5.1)	4.43 (0.85)	2.90 (1.51)	Active drug
2	Japan	213	39.3 (13.5)	51.2	24.0 (4.9)	4.11 (0.78)	2.57 (1.25)	Active drug
3	United States	447	38.8 (11.6)	58.4	23.5 (3.2)	4.28 (0.51)	2.36 (1.21)	Placebo
4	United States	501	41.1 (11.7)	68.3	21.5 (3.5)	4.36 (0.57)	—	None (1-arm)
5	Japan	197	40.0 (11.7)	54.2	21.7 (3.5)	4.04 (0.55)	—	Active drug
6	Japan	153	48.0 (14.3)	62.1	23.3 (5.7)	—	2.84 (1.54)	Active drug
7	Japan	200	45.0 (14.3)	53.0	23.2 (6.0)	—	2.48 (1.37)	Active drug

Means (SD) are shown.
CGI-C indicates CGI Change scale; CGI-S, CGI Severity scale.

severely ill, and 7 = among the most extremely ill patients. The CGI-C assesses the patient's improvement or worsening since the start of the study using the following scores: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. We did not distinguish between patients on active drugs and those on placebo because pooling them can give wider variation in scores and hence finer characterization of anchor points. On average, the CGI-S decreased from 4.3 (SD, 0.64) to 2.4 (SD, 1.3). The CGI-C was judged to be 2.6 (SD, 1.4).

We first calculated Spearman rank correlation coefficients between HAM-D scores and CGI-S scores at baseline and at end of treatment and between absolute and relative changes in HAM-D scores and CGI-C scores. Substantial correlations are the prerequisite of the following analyses to link HAM-D scores and CGI scores.

When substantial correlations greater than 0.7 were noted, CGI scores were equated to the HAM-D scores by finding, for each value on the CGI, the corresponding value on the HAM-D. In other words, we interpreted values as corresponding if approximately the same proportion of patients scored above and below a particular value, as was done in the pioneering works on this topic by Bandelow et al[9] and Leucht et al.[2,10] For example, if 54% of the patients scored 2 or less on the CGI-S and 54% scored 7 or less on the HAM-D, then a CGI-S of 2 or less corresponds to a HAM-D of 7 or less.

All the analyses were performed with the modified intention-to-treat sample (ie, with all patients who took at least 1 dose of the study drug and had 1 postbaseline assessment and for whom the last observation carried forward was used in case of dropouts).

The correlation between HAM-D and CGI-S at baseline was only moderate at 0.43 (n = 1561; $P < 0.001$), probably because the minimum severity requirement of the eligibility criteria limited variability among the included patients. We reasoned that this would limit characterization of HAM-D scores especially toward the milder end and therefore decided to limit our analyses concerning the CGI-S to the end point data only, which correlated at 0.87 (n = 1561; $P < 0.001$) with HAM-D. On the other hand, because of the high correlations between CGI-C and both absolute and relative reductions in HAM-D scores (−0.88, n = 1211; $P < 0.001$; and −0.90, n = 1211; $P < 0.001$, respectively), we felt justified in linking CGI-C with both methods of quantifying changes.

The correspondences between CGI-S and HAM-D scores, based on end point data, indicated that HAM-D scores between 0 and 3 signify "normal/not at all ill," those between 4 and 7 "borderline ill," those between 8 and 15 "mildly ill," those between 16 and 26 "moderately ill," and those at 27 or more "markedly or severely ill." Because there were only a small number of subjects rated as markedly or severely or extremely ill, to interpret the HAM-D scores reliably, we needed to collapse these strata.

The correspondences between CGI-C scores and absolute reductions of HAM-D scores or relative reductions in HAM-D scores in percentages were then analyzed. The number of patients who got much or very much worse was small, and therefore, we needed to collapse these strata too. A patient needs to have a reduction in his/her HAM-D scores by 18 points or more or by 73% or more to be rated "very much improved," by 11 to 17 points or by 46% to 72% to be rated "much improved," by 4 to 10 points or by 15% to 45% to be rated "minimally improved," but reductions by zero to 4 points or by −5% to 14% would be regarded as "no change," and increase by 1 or more points or 6% or more would be regarded as worsening.

DISCUSSION

This is the first study to provide an evidence-based guideline for interpreting HAM-D scores both cross-sectionally for severity and longitudinally for change in severity. The HAM-D was developed in the late 1950s to assess the effectiveness of then newly developed antidepressants and has since quickly become the standard measure to assess depression both in clinical trials and daily practices across the world.[11] After more than 40 years of use, despite some criticisms,[12] it still remains the most commonly used measure of depression and arguably the most often used psychiatric rating scale for mental disorders.

Cross-sectionally, our findings largely confirmed the extant consensus definitions. Scores of 7 or less would mean "not ill" or "asymptomatic." Scores between 8 and 15 would signify "mildly ill." Oftentimes, such people would fall below the diagnostic threshold for major depression according to

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and likely not benefit from antidepressant treatment.[13] Scores between 16 and 26 would correspond with "moderately ill" patients who would satisfy diagnostic criteria for major depression. This threshold coincides very well with the usual practice of requiring at least 16 or so to be included in a clinical trial.

Longitudinally, clinicians are justified in rounding up our findings and interpreting reduction by 75% or more as "very much improved" and reduction by 50% to 75% as "much improved." On the other hand, reduction between 0% and 50% would constitute "minimal improvement" that may very well not be clinically meaningful. We can also interpret the obtained scores from a different angle and conclude that an absolute reduction by 4 to 10 points is not clinically significant, but we need 11 or more point change to judge the patient to have improved. The minimal important difference[14] for the HAM-D is therefore 11 points.

It is very interesting to note the close correspondences between the absolute change scores and the relative change scores. It is easy to see that a 5-point reduction from 30 to 25 would not be equal to the same 5-point reduction from 5 to zero, just as a 50% reduction from 30 to 15 would not be equal to the same 50% reduction from 10 to 5. In actual practices, clinicians need to balance the consideration for both the absolute and the relative changes.

Our results can and should also be interpreted in terms of appropriate definitions of remission and response for major depression. "Remission" clearly corresponds with CGI-S scores of 1 (not at all ill) or 2 (borderline mentally ill) and "response" with CGI-C scores of 1 (very much improved) or 2 (much improved).[9] Remission should then be defined as scoring 7 or less on the HAM-D, and this should constitute the primary treatment goal for major depression. Response would be defined as 46% or more reduction in HAM-D scores, and the tradition of taking 50% or greater reduction as signifying response seems justified.

Some possible weaknesses of the present study should be noted. First, the same raters assessed the HAM-D and CGI scales, and thus, their ratings were not independent in the 5 trials conducted in Japan. Unless the raters mechanically converted the HAM-D scores into CGI scores and if instead they rated the global impression of the patients' depression severity or change in severity as instructed by the protocols, this should not undermine the validity of our anchor-based approach. As a matter of fact, the correlations between HAM-D and CGI-S at baseline or reduction in HAM-D and CGI-C at posttreatment were very similar between Japanese trials and those conducted in the United States, where the HAM-D and CGI were rated by independent raters (0.86 and −0.90 in Japan, and 0.84 and −0.83 in the United States, respectively). Second, analyses with CGI-S were conducted only with end point scores because of limited range of baseline scores. There were so few severely depressed patients in the sample, as can be expected in clinical trials, but it limits our understanding of the HAM-D toward the most severe end of depression spectrum. Third, despite the large sample size, our data set did not include enough number of patients who got "much or very much worse." The interpretability of HAM-D scores when the patient's status deteriorates is therefore not as secure as when it improves. On the other hand, strengths of our study include, first and foremost, the data-driven approach based on a very large sample of patients pooled from international and multicenter clinical trials. This increases the generalizability of our recommendations.

In conclusion, we established the first evidence-based guidelines for interpreting the widely used HAM-D. It is advised that similar guidelines become available to clinicians for many more commonly used psychiatric rating scales to increase their interpretability, so that they can easily interpret not only the obtained results in their clinical practices but also the published findings in the medical literature.

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REFERENCES

1. Furukawa TA, Jaeschke R, Cook D, et al. Measurement of patients' discomfort, distress and disability. In: Guyatt G, Drummond R, eds. *Users' Guides to the Medical Literature.* 2nd ed. Chicago: AMA Press. In press.
2. Leucht S, Kane JM, Kissling W, et al. Clinical implications of Brief Psychiatric Rating Scale scores. *Br J Psychiatry.* 2005; 187:366–371.
3. Guy W. *ECDEU Assessment Manual for Psychopharmacology.* Rockville, MD: US Department of Health and Human Services; 1976.
4. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry.* 1991;48:851–855.
5. Furukawa TA, McGuire H, Barbui C. Meta-analysis of effects and side effects of low dosage tricyclic antidepressants in depression: systematic review. *BMJ.* 2002;325:991–995.
6. Spielmans GI, McFall JP. A comparative meta-analysis of Clinical Global Impressions change in antidepressant trials. *J Nerv Ment Dis.* 2006;194:845–852.
7. Furukawa TA, Streiner DL, Azuma H, et al. Cross-cultural equivalence in depression assessment: Japan-Europe-North American study. *Acta Psychiatr Scand.* 2005;112:279–285.
8. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23:56–62.
9. Bandelow B, Baldwin DS, Dolberg OT, et al. What is the threshold for symptomatic response and remission for major depressive disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder? *J Clin Psychiatry.* In press.
10. Leucht S, Kane JM, Kissling W, et al. What does the PANSS mean? *Schizophr Res.* 2005;79:231–238.
11. Bech P, Coppen A, eds. *The Hamilton Scales.* Berlin: Springer-Verlag; 1990.
12. Bagby RM, Ryder AG, Schuller DR, et al. The Hamilton Depression Rating Scale: has the gold standard become a lead weight? *Am J Psychiatry.* 2004;161:2163–2177.
13. Paykel ES, Freeling P, Hollyman JA. Are tricyclic antidepressants useful for mild depression? A placebo controlled trial. *Pharmacopsychiatry.* 1988;21:15–18.

14. Redelmeier DA, Guyatt GH, Goldstein RS. Assessing the minimal important difference in symptoms: a comparison of two techniques. *J Clin Epidemiol.* 1996;49:1215–1219.

Are the Effects of Rater Training Sustainable?

Results From a Multicenter Clinical Trial

To the Editors:

With the high rate of failed and negative trials,[1] the importance of the quality of the clinical assessments conducted in these trials has recently become the focus of much attention in the literature. Studies showing the relationship between good clinical interviews and signal detection illustrate the impact that poorly conducted interviews can have on study outcome.[2,3] Other studies have found that the most ratings in clinical trials, in general, are of fair or poor quality, demonstrating the need for intervention in this area.[3,4] Several rater training programs have recently been developed that have successfully improved raters' clinical skills before the study initiation.[5,6] Although these studies found that raters' clinical skills could be tested and improved before being certified to rate in a study, there has been no evidence, to date, on whether these skills are maintained during the course of a trial. The current study examined this issue in a multicenter depression trial.

Thirty-one raters from 15 sites went through a training and certification process on the Hamilton Rating Scale for Depression (HAMD) and Anxiety (HAMA)[7,8] before initiating the trial. All raters were required to have prior clinical experience with depressed patients and documented experience administering the HAMD, the primary outcome measure in the trial. Raters' education ranged from MDs and PhDs to BA- and MA-level clinicians.

The certification process consisted of 2 components, didactic training/testing and applied training/testing, and is described in detail elsewhere.[5,6] To be certified to rate patients in the trial, raters had to achieve passing scores on both components. The didactic component consisted of a Web-based tutorial on the HAMD, a handout on scoring conventions for the HAMA, and a 20-item multiple-choice posttest. The applied component consisted of live observation of the trainee conducting a HAMD and HAMA interview with a depressed patient via a 3-way teleconference. The trainer provided feedback to the rater on their interviewing technique and on their scoring rationale and rated the trainee's applied performance using the Rater Applied Performance Scale[9] (RAPS). Trainees who received a failing score on the RAPS scale (ie, mean score of fair or poor [see below]) were required to conduct another interview, incorporating the feedback given. Trainees were given a total of 3 opportunities to pass the applied component. If the trainee failed on the third interview, he or she was excluded from rating patients in the trial. The Structured Interview Guide for the HAMA and HAMD[10] was used in the training.

To evaluate whether trainees retained the skills learned during certification and to prevent rater drift, raters were required to be retested on their applied skills approximately halfway through the study (ie, roughly 12 months later). A similar assessment procedure was used as during their prestudy certification, that is, raters interviewed a depressed patient while being observed and evaluated by a trainer via 3-way teleconference. Raters who failed the midstudy evaluation were given feedback and additional opportunities to pass, as was done in the original training.

Results of the initial training are detailed elsewhere[6] and will be summarized here. A significant improvement was found after the initial training in both the trainees' didactic knowledge of scoring conventions and the trainees' applied clinical interviewing skills. On the initial applied training, 57% passed on their initial attempt (prior to any feedback), 30% passed on their second attempt, and 7% on their third attempt, and 7% failed all 3 attempts and were excluded from participating in the study. For persons who failed their first applied test in their initial training, their RAPS score improved significantly after feedback on their second attempt, from 9.05 to 11.58, $P = 0.001$. Similarly, for those who failed their second attempt, RAPS scores improved significantly after feedback on their third attempt, from 9.0 to 11.0, $P = 0.033$. The mean RAPS score for all raters who were certified to rate in the study on their final (passing) attempt was 12.22 (SD = 1.75) (maximum possible score = 16). A score of 14.5 to 16 is roughly equivalent to a rating of excellent performance for all RAPS dimensions, 10.5 to 14.4 is good, 6.5 to 10.4 is fair, and less than 6.5 is poor.

At midpoint, the mean RAPS score decreased significantly from their initial posttraining scores, from 12.22 to 10.68 (SD = 2.64), $t_{30} = 2.976$, $P = 0.006$. This change is clinically significant, as it represents a change from a solid to a borderline "good." The largest decreases were on the RAPS dimensions of neutrality (0.32 point) and follow-up (0.26 point). Eighteen raters (58%) passed the midpoint evaluation on the first try. Of the 13 raters (42%) who did not pass, the mean RAPS score significantly improved following feedback, from a mean of 7.82 on their initial attempt to a mean of 12.36 on their second attempt, $t_{10} = 5.590$, $P < 0.0001$. Two raters failed the second attempt, but passed on their third and final try, with the mean RAPS score improving from 9.5 on time 2 to 12.0 on time 3.

Results were also analyzed by educational degree. Raters with MD or PhD degrees (n = 12) did not have a significant drop in RAPS scores from prestudy certification to midpoint (12.25–11.50, $t_{11} = 0.828$, $P = 0.425$), whereas those with highest degree being MA or BA (n = 14) did have a significant drop (12.43–10.14, $t_{13} = 3.04$, $P = 0.009$). The mean drop in the latter group (2.29 points) was more than 3 times as large as the drop in the MD/PhD group (0.75 points).

DISCUSSION

The results indicate that although rater training can successfully improve raters' applied clinical skills, these skills can erode over the course of a trial. On the other hand, follow-up testing and training may be successful in re-establishing these skills. We did not do testing at study termination, and thus, we do not know if the reinforcement of the second intervention led to

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Brief report

Regional cerebral glucose metabolism in patients with secondary depressive episodes after fatal pancreatic cancer diagnosis

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Abstract

Background: Secondary depression is common in the clinical oncology setting after pancreatic cancer diagnosis, following which the patients have to face the fact that they have a cancer with an extremely poor prognosis. However, the specific pathophysiology remains unclear. The present study examined the regional cerebral glucose metabolism using F18-fluorodeoxyglucose (F18-FDG) positron emission tomography (PET) in antidepressant-naïve pancreatic cancer patients with a depressive episode after their cancer diagnosis and before their cancer treatment.

Methods: Regional cerebral glucose metabolism in pancreatic cancer patients without any antidepressant medication after the cancer diagnosis was measured with F18-FDG PET. A depressive episode after the cancer diagnosis was defined as including major and minor depressive episodes, and was diagnosed using the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV). The prefrontal and limbic regions were the primary regions-of-interest, and an uncorrected value of $p<0.005$ was used as significant.

Results: Six of 21 pancreatic cancer patients were diagnosed as having a depressive episode. Significantly higher glucose metabolism in depressed patients was found in the subgenual anterior cingulate cortex (sACC) (uncorrected $p=0.002$).

Limitations: There was a small number of subjects, and there were no healthy controls.

Conclusions: The higher metabolism in the sACC may be associated with the pathophysiology of secondary depressive episodes in patients following pancreatic cancer diagnosis.

Keywords: Depression; Anterior cingulate cortex; Positron emission tomography; Pancreatic cancer; Regional cerebral metabolic rate of glucose

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1. Introduction

Pancreatic cancer is a refractory malignant tumor, and has a 5-year survival rate of only 4%. More than 30,000 patients died from pancreatic cancer in the year 2006 in the USA. Psychiatric symptoms, especially depression and anxiety, in pancreatic cancer patients have been focused on by clinicians, as several textbooks describe the association of psychiatric symptoms with pancreatic cancer. Previous studies reported 18–50% of pancreatic cancer patients experienced depression (Bernhard and Hurny, 1998; Green and Austin, 1993).

Although several serum substrates secreted by pancreatic cancer have been postulated to be involved in the pathophysiology of depression (Bernhard and Hurny, 1998; Green and Austin, 1993), no clear associations have so far been made in human. On the other hand, depressive episodes in pancreatic cancer patients may reflect the psychological response to the knowledge to having a tumor whose extremely poor prognosis is well known. However, brain neuron-circuitry related to depressive episodes in patients after pancreatic cancer diagnosis has been unclear.

Recent developments in neuroimaging techniques have revealed the involvement of neural mechanisms in a depressive episode. Previous studies have shown the involvement of the prefrontal and limbic regions (Drevets, 2001) and corticolimbic dysregulation in depression (Mayberg et al., 1999). Although findings have been variable, decreased dorsolateral and subgenual prefrontal and increased amygdala cerebral metabolic rates tend to be seen in patients with depression. A previous review article showed that prefrontal hypometabolism may be a common pathway to depressive symptoms in primary (psychiatric) and secondary (to neurological disorders) depression (Mayberg, 1994). However, potential differences in the depression subtype may cause different patterns of neural activity. An involvement of the potential serum substrates secreted by pancreatic cancer with depressive episodes may suggest a different pathophysiology. In addition, the depressive episodes in cancer patients have generally been assumed to be reactive and of short duration (Chochinov, 2001), suggesting that they have a different pathophysiology.

Although serum substrates secreted by pancreatic cancer and/or psychological stressor have been postulated to be associated with the depressive episodes in pancreatic cancer patients, details of the mechanisms have been unclear. Investigation of the neural circuitry is one of the useful strategies to reveal the possible mechanisms of depressive episodes in pancreatic cancer patients. In the present study, we performed a preliminary investigation using positron emission tomography (PET) to examine the regional cerebral metabolic rate of glucose (rCMRgluc) in the prefrontal and limbic regions among pancreatic cancer patients with a depressive episode after their cancer diagnosis.

2. Methods

2.1. Subjects

This study was approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center, Japan, and was performed after obtaining written informed consent from the patients. The inclusion criterion of the subject sampling was clinically diagnosed pancreatic cancer patients after disclosure of the diagnosis before anticancer treatment who were going to undergo positron emission tomography (PET) to evaluate the clinical stage of the cancer as a clinical investigation. Exclusion criteria were (1) <18 years old; (2) having neurological and/or Axis I psychiatric disorders defined by the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) except for mood and anxiety disorders; (3) having a mass legion in the brain; (4) having a blood sugar level higher than 120 mg/dl; (5) receiving a hypoglycemic agent; (6) having any physical function that interfered with daily life, as assessed by performance status; and (9) a cognitive impairment defined as a score of less than 24 on the Mini-Mental State Examination (Mori et al., 1985).

2.2. Procedure

Subject sampling was performed among inpatients who were going to undergo PET for pancreatic cancer before their treatment in the National Cancer Center Hospital East. Diagnosis of pancreatic cancer was done as a clinical diagnosis, but not as a pathological diagnosis. After their attending physician had booked their PET examination for clinical staging of their pancreatic cancer and at least within 2 days before the PET examination, trained psychiatrists (EY, MK) performed an interview including the Structured Clinical Interview for DSM-IV-Axis I Disorder to determine whether the subjects had a depressive episode. We defined the *depressive episode* on the basis of criteria of the major and/or minor depression of the DSM-IV, because, not only major depression, but a minor depressive episode can also have a negative impact in the same manner as a major depressive episode (Evans et al., 1999). In addition, a study into depressive symptomatology has indicated continuity of minor depressive episodes to major depressive episodes (Kendler and Gardner, 1998).

Table 1
Demographic and medical backgrounds of the patients

	Cancer patients		Statistic value	p
	With depressive episode $n=6$	Without depressive episode $n=15$		
Age (years old)[a]	69.5±3.3	62.5±1.7	$t=2.05$	$p=0.06$
Gender[b]: male	3 (50%)	9 (67%)	$\chi^2=0.18$	$p=0.52$
Height (cm)[a]	158.2±3.7	149.7±9.8	$t=0.54$	$p=0.60$
Weight (kg)[a]	55.5±3.4	53.8±1.9	$t=0.48$	$p=0.64$
Handedness (no. of patients)				
right	6 (100%)	15 (100%)	–	–
Education (years)[a]	12.8±1.1	12.9±0.7	$t=0.03$	$p=0.98$
PS (no. of patients)[b]				
0	6 (100%)	12 (80%)	$\chi^2=1.40$	$p=0.34$
1	0 (0%)	3 (20%)	–	–
Clinical stage[b]				
II	1 (17%)	1 (7%)	$\chi^2=0.50$	$p=0.50$
III–IV	5 (83%)	14 (93%)	–	–
Pain[c]	3 (0–7)	1 (0–6)	$U=29.0$	$p=0.24$
Fatigue[c]	2 (1–6)	1 (0–8)	$U=26.0$	$p=0.15$
Shortness of breath[c]	0.5 (0–2)	0 (0–1)	$U=30.5$	$p=0.27$
Appetite loss[c]	1.5 (0–2)	1 (0–10)	$U=43.5$	$p=0.91$
Nausea[c]	0 (0–0)	0 (0–8)	$U=39.0$	$p=0.68$
Opioids use (no. of patients)[b]	2 (33%)	3 (20%)	$\chi^2=0.42$	$p=0.45$
Psychotropic medication	1 (17%)[d]	1 (7%)[d]	$\chi^2=0.50$	$p=0.50$
Anticonvulsant medication	0 (0)	0 (0)	–	–
BS before PET (mg/dl)[a]	102±5.4	103±2.9	$t=0.23$	$p=0.82$
FDG injection (MBq)[a]	258.7±9.5	267.6±4.1	$t=1.03$	$p=0.32$
HDRS score[e]	10.8 (6–15)	5.7 (0–13)	$U=11.5$	$p<0.01$
STAI score[e]	88.3 (84–98)	75.1 (59–111)	$U=16.0$	$p=0.02$
IES-R score[e,f]	25.0 (14–44)	8.2 (0–28)	$U=11.5$	$p=0.01$

No.: number; PS: performance status; BS: blood sugar; PET: positron emission tomography; FDG: F18-fluorodeoxyglucose; HDRS: the Hamilton Depression Rating Scale 17 item version; STAI; the State and Trait Anxiety Inventory; IES-R; the Impact of Event Scale-Revised.

[a] Mean±standard deviation and t and p values of the Student's t-test.

[b] Number of patients (percentage) and χ^2 and p values of the χ^2 test.

[c] Pain, fatigue, shortness of breath, and nausea were measured by using the MDASI and indicated median (minimum−maximum) score, and U and p value of the Mann-Whitney U test.

[d] One subject in the depressed group used alprazolam and one subject in the nondepressed group used lormetazepam.

[e] Median (minimum−maximum) score, and U and p value of the Mann-Whitney U test.

[f] Number of cancer patients without depressive episode was 13.

The reliability of the diagnostic interview was tested by having another interviewer as a second rater (kappa=1.0, $n=21$). Medical data were collected by chart review, and demographic data were collected by a structured interview. The Hamilton Depression Rating Scale 17 item version (HDRS) was used to measure depression severity (Hamilton, 1960). To evaluate physical symptoms, the M.D. Anderson Symptom Inventory-Japanese version (MDASI) (Okuyama et al., 2003) was used to measure pain, fatigue, shortness of breath, appetite loss, nausea, and vomiting, rated using a 0-to-10 numerical system. The Impact of Event Scale-Revised, a 22-item self-rating questionnaire, was used (Asukai et al., 2002) to assess the level of symptomatic reaction to a traumatic experience i.e., disclosure of cancer diagnosis. The score ranges from 0 to 88. The State and Trait Anxiety Inventory (Spielberger et al., 1970), a 40-item self-rating questionnaire designed to evaluate state- and trait-anxiety, was used to measure the anxiety level. The score ranges from 40 to 160.

2.3. Measurement of regional glucose metabolism by PET

Under resting conditions in a dark room for thirty minutes after an injection of F18-fluorodeoxyglucose (FDG) (5 MBq/kg), 10-min transmission with ^{68}Ge and 20 min emission scans of the brain were performed using a GE ADVANCE NXi (GE Medical Systems, Milwaukee). The spatial resolution of this scanner is 4.8 mm full width at half maximum. Whole body PET scans to evaluate the clinical stage of pancreatic cancer were performed after the brain scans. Summed images were used for data analysis. Preprocessing of scanned images was done using SPM2 software (Wellcome Department of Cognitive Neurology, London). Images were normalized

to a template, globally normalized, and smoothed using a 12-mm Gaussian kernel.

2.4. Statistical analyses

Comparisons of the background and medical factors were performed by the Student's t-test, the Mann-Whitney U test, or the χ^2 test between patients with a current depressive episode and those without an episode. rCMRgluc was compared between the two groups on the SPM2 software using an ANCOVA model with age and gender as nuisance variables. A statistical p value of the comparison was uncorrected $p<0.005$ in the regions of interest (ROIs), including the prefrontal and limbic regions. Other brain regions were compared using $p<0.001$ as a reference, with no discussion of the results.

3. Results

Six of the 21 pancreatic cancer patients were diagnosed as having a depressive episode after pancreatic cancer diagnosis. Two had major depressive episodes and 4 had minor depressive episodes. In the 6 patients with a current depressive episode, none had any history of a major or minor depressive episode before their cancer diagnosis. In the remaining 15 cancer patients without a current depressive episode, one patient had a history of minor depression before the cancer diagnosis. The duration of the episode up to the time of the PET was less than 6 weeks (mean duration was 3 weeks). All of the episodes developed after the disclosure of the pancreatic cancer diagnosis by the patients' physicians. None of the patients had been diagnosed as having a current/past history of anxiety disorders, including post-traumatic stress disorder (PTSD), substance-use disorders, or bipolar disorder. Table 1 shows no significant difference in demographic and medical factors between the two groups. In the psychological factors, the scores of the HDRS, the STAI, and the IES-R were significantly different between the groups. Amongst the ROIs, the subgenual anterior cingulate cortex (sACC) had a significantly higher rCMRgluc (uncorrected $p=0.002$, $t=2.89$) (Fig. 1). The xyz coordinate of the MNI space was [−8 32 −10]. Sub-analyses showed no significant correlations between the rCMRgluc values at the coordinate and the HDRS scores ($r=0.259$, $p=0.285$) or the STAI scores ($r=0.116$, $p=0.635$) ($n=21$). Among the patients with depression, however, the partial correlation coefficients of rCMRgluc at the coordinate were $r=-0.992$ ($p=0.008$) for the HRSD scores and $r=-0.872$ ($p=0.128$) for the STAI scores ($n=6$). There was no region amongst the other ROIs which had a significantly lower rCMRgluc. Out with the ROIs, the region which did have a significantly lower rCMRgluc in the depressed patients was the cerebellum (uncorrected $p<0.001$, $t=3.23$, and size=30 voxels), of which the xyz coordinates of the MNI template were [20 −86 −32]. No region outside the ROIs had a significantly higher rCMRgluc.

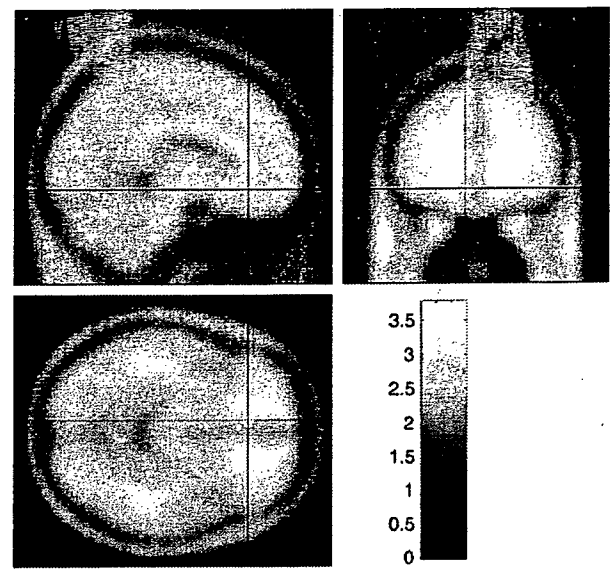

Fig. 1. Statistical parametric map illustrating a higher regional cerebral metabolic rate of glucose (uncorrected $p<0.005$) in the left subgenual anterior cingulate under resting condition in pancreatic cancer patients with the first depressive episode after cancer diagnosis compared with those without a depressive episode. The color bar indicates the t value.

4. Discussion

The present study showed a significantly higher rCMRgluc in the sACC in antidepressant-naive pancreatic cancer patients with a depressive episode after their diagnosis of cancer, before their cancer treatment.

To the best of our knowledge, no study has yet demonstrated rCMRgluc in depressed pancreatic cancer patients. A previous study demonstrated an inverse correlation between depressive mood measured by a self-rating scale and rCMRgluc of only the right caudate under resting condition in 8 cancer patients with lung, breast, colon, or prostate cancer before or after cancer treatment (Tashiro et al., 2001), which was inconsistent with the result of the present study. This inconsistency may be attributed to the differences in timing of the assessment, the use of an anti-cancer chemotherapeutic agent, and/or the characteristics of depression including some difference in the definition of "depression" between the two studies. On the other hand, in the previous study, a self-reported anxiety scale was positively correlated with

the metabolism of the anterior cingulate cortex, which is near the principal ROI in the present study. The STAI score to measure the anxiety was significantly different between the two groups in the present study. Anxiety could have contributed significantly to the findings in this group of generally mildly depressed patients.

Giving the reciprocal connections of the sACC with the orbital cortex, hypothalamus, amygdala, and accumbens, which are implicated in emotional behavior (Drevets, 2001), the result of the present study indicating the association of the sACC with a depressive episode in pancreatic cancer patients seems plausible. Many of the previous neuroimaging studies in major depression demonstrated lower glucose metabolism in the subgenual prefrontal cortex (Drevets, 2001). Although the definition of depression in the present study using a combination of major and minor depression was different from that of previous studies, the indication in the present study of a higher metabolism at the sACC was a possible inconsistency. Several reasons can be considered. Drevets et al. reported lower glucose metabolism in the region, which actually turned to be a higher glucose metabolism after adjustment for the smaller volume of the region in subjects with familial major depression (Drevets, 2001). Because the present study did not measure the volume of the regions, further study is needed to confirm the real activity after adjusting for the volume.

The other explanation for the inconsistent higher metabolism may be based on the findings in patients with PTSD indicating a higher metabolism in the regions (Shin et al., 1997) and in healthy non-depressed subjects during experimentally induced sadness in which blood flow increases in the regions were indicated (Damasio et al., 2000; Mayberg et al., 1999). Given the high comorbidity rate of depression in PTSD (Breslau et al., 2000; Kessler et al., 1995), a PTSD-like pathophysiology may be associated with depression after pancreatic cancer diagnosis. In fact, the total score of the IES-R was significantly higher in the depressed group compared with the non-depressed group. In addition, the PET scans for the investigation of pancreatic cancer may cause distressing recollections about the cancer-related traumatic event. Rumination may be related to the higher activity of sACC observed in the present study. This may be a specific finding in depression in pancreatic cancer patients.

Although the primary result of the present study indicated an increased rCMRgluc in the sACC of depressed subjects, the sub-analysis showed a paradoxical association between an increased rGMRgluc and a lower HDRS score. rCMRgluc in the sACC may not be linearly correlated with the severity of depression. A second study with a larger sample size is needed to clarify this point.

Taking the substrates secreted by pancreatic cancer into account, a different pathophysiology of depression in pancreatic cancer patients may exist, in addition to the psychological response. The fact that all of the depressive episodes had developed serially after the distressing event of disclosure of the cancer diagnosis indicates the possibility that psychological distress plays a role in developing the depressive episode. However, the possible effect of substances secreted by pancreatic cancer on the development of the depressive episode and increased metabolism in the sACC could not be excluded.

The present study has the following limitations: (1) the small number of depressed subjects; (2) the cross-sectional study design and the unclear causality of rCMRgluc; (3) patient use of opiates as a potential confounding factor; (4) the lack of a healthy control group; (5) the use of a clinical, rather than a pathological, diagnosis of pancreatic cancer; (6) the trend towards depressed patients being older than nondepressed patients; (7) the generally mild degree of depression in the depressed patients; and (8) the use of normalized rather than absolute rCMRgluc values.

The present study indicated a higher glucose metabolism in the sACC in pancreatic cancer patients with a depressive episode after their cancer diagnosis. However, a large sample size study with a longitudinal design is needed.

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References

Asukai, N., Kato, H., Kawamura, N., Kim, Y., Yamamoto, K., Kishimoto, J., Miyake, Y., Nishizono-Maher, A., 2002. Reliability and validity of the Japanese-language version of the impact of event scale-revised (IES-R-J): four studies of different traumatic events. J. Nerv. Ment. Dis. 190, 175–182.

Bernhard, J., Hurny, C., 1998. Gastrointestinal cancer. In: Holland, J.C. (Ed.), Psycho-oncology. Oxford university press, New York, pp. 324–339.

Breslau, N., Davis, G.C., Peterson, E.L., Schultz, L.R., 2000. A second look at comorbidity in victims of trauma: the posttraumatic stress disorder-major depression connection. Biol. Psychiatry 48, 902–909.

Chochinov, H.M., 2001. Depression in cancer patients. Lancet Oncol. 2, 499–505.

Damasio, A.R., Grabowski, T.J., Bechara, A., Damasio, H., Ponto, L.L., Parvizi, J., Hichwa, R.D., 2000. Subcortical and cortical brain activity during the feeling of self-generated emotions. Nat. Neurosci. 3, 1049–1056.

Drevets, W.C., 2001. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. Curr. Opin. Neurobiol. 11, 240–249.

Evans, D.L., Staab, J.P., Petitto, J.M., Morrison, M.F., Szuba, M.P., Ward, H.E., Wingate, B., Luber, M.P., O'Reardon, J.P., 1999. Depression in the medical setting: biopsychological interactions and treatment considerations. J. Clin. Psychiatry 60 (Suppl 4), 40–55 (discussion 56).

Green, A.I., Austin, C.P., 1993. Psychopathology of pancreatic cancer. A psychobiologic probe. Psychosomatics 34, 208–221.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.

Kendler, K.S., Gardner Jr, C.O., 1998. Boundaries of major depression: an evaluation of DSM-IV criteria. Am. J. Psychiatry 155, 172–177.

Kessler, R.C., Sonnega, A., Bromet, E., Hughes, M., Nelson, C.B., 1995. Posttraumatic stress disorder in the National Comorbidity Survey. Arch. Gen. Psychiatry 52, 1048–1060.

Mayberg, H.S., 1994. Frontal lobe dysfunction in secondary depression. J. Neuropsychiatry Clin. Neurosci. 6, 428–442.

Mayberg, H.S., Liotti, M., Brannan, S.K., McGinnis, S., Mahurin, R.K., Jerabek, P.A., Silva, J.A., Tekell, J.L., Martin, C.C., Lancaster, J.L., Fox, P.T., 1999. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am. J. Psychiatry 156, 675–682.

Mori, E., Mitani, Y., Yamadori, A., 1985. Usefulness of a Japanese version of the Mini-Mental State in neurological patients. Shinkeishinrigaku 1, 82–90.

Okuyama, T., Wang, X.S., Akechi, T., Mendoza, T.R., Hosaka, T., Cleeland, C.S., Uchitomi, Y., 2003. Japanese version of the MD Anderson Symptom Inventory: a validation study. J. Pain Symptom Manage. 26, 1093–1104.

Shin, L.M., Kosslyn, S.M., McNally, R.J., Alpert, N.M., Thompson, W.L., Rauch, S.L., Macklin, M.L., Pitman, R.K., 1997. Visual imagery and perception in posttraumatic stress disorder. A positron emission tomographic investigation. Arch. Gen. Psychiatry 54, 233–241.

Spielberger, D., Gorsuch, L., Lushene, E., 1970. STAI manual. Consulting Psychologists Press, Palo Alto.

Tashiro, M., Itoh, M., Kubota, K., Kumano, H., Masud, M.M., Moser, E., Arai, H., Sasaki, H., 2001. Relationship between trait anxiety, brain activity and natural killer cell activity in cancer patients: a preliminary PET study. Psychooncology 10, 541–546.